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A NOTE ON THE ASSAY OF FORMALDEHYDE.

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It has been shown by Williams [1] that the two different types of methods for estimating formaldehyde, namely, those dependent on the oxidation of the formaldehyde and those dependent on its forming condensation products, do not yield concordant results. In explanation of this discrepancy, Williams advances the view that "either the condensation reactions are not complete or a small part of the formic acid is oxidized farther." He also reaches the conclusion that the hydrogen peroxide method is the most satisfactory for strong, impure solutions; while "the potassium cyanide method is recommended for dilute, impure solutions." Recently, the writer has had occasion, in connection with the study of embalming fluids [2] which has been in progress in this laboratory, to make a comparatively large number of determinations of the quantity of free formaldehyde in these fluids. Owing to the possible presence in such fluids of substances other than formaldehyde which on oxidation will yield acids (thus rendering the hydrogen peroxide method inapplicable), or other reducing substances (thus invalidating the iodometric method), it was found necessary to resort to one of the condensation methods, and the potassium cyanide method was chosen. It became of interest, therefore, to look into the points raised by Williams as to the discrepancy of the results obtained by the oxi-

[1] *Jour. Amer. Chem. Soc.*, **27**, 596-601 (1905).

[2] It is expected that the results of this study will shortly be published as a Hygienic Laboratory Bulletin.

dation and condensation methods and the possible incompleteness of the condensation reactions.

The methods investigated by Williams were those which are most generally recommended for the determination of formaldehyde, namely, the ammonia method of Legler,[3] the hydrogen peroxide method of Blank and Finkenbeiner,[4] and the iodometric and potassium cyanide methods of Romijn.[5] His conclusion that the results obtained by the condensation methods are lower than those obtained by the oxidation methods, is in harmony with the previous work of Smith,[6] who also found that, as compared with the Legler method, "the hydrogen peroxide method almost invariably gave higher results." Smith also seems to hold the view that the potassium cyanide method is applicable to dilute solutions only, since he refers to the KCN method as a "method which is applicable to solutions containing but small quantities of formaldehyde;" and while he concludes that "the iodometric and potassium cyanide methods give good results on dilute solutions," he adds that "it should be remembered that in diluting strong solutions to the range of these methods, a small error in weighing may be considerably multiplied." Apparently influenced by this suggestion of Smith, many authors on analytical chemistry do not recommend the potassium cyanide method except in the case of dilute solutions. Thus Leffmann and Beam,[7] referring to the work of Smith, state that for the determination of formaldehyde the choice of the method "will depend on the strength of the solution," recommending the iodine method of Romijn in the case of moderately strong solutions and the potassium cyanide method for dilute solutions. Likewise, from Schimpf,[8] who also refers to the work of Smith, one gains the information that "the Blank and Finkenbeiner method is very satisfactory for strong solutions" and "the iodometric and potassium cyanide methods give good results on dilute solutions." Similarly, Leach[9] omits the potassium cyanide method as a suitable method for determining formaldehyde in the commercial preservative, although list-

[3] *Ber.*, **16**, 1333–1337 (1883).
[4] *Ber.*, **31**, 2979–2981 (1898).
[5] *Zeit. anal. Chem.*, **36**, 18–24 (1897).
[6] *Jour. Amer. Chem. Soc.*, **25**, 1028–1035 (1903).
[7] Leffmann and Beam: Food Analysis, 2d ed., p. 84 (1905).
[8] Schimpf: Manual of Volumetric Analysis, 5th ed., pp. 644–645 (1909).
[9] Leach: Food Inspection and Analysis, 2d ed., p. 819 (1907).

ing the iodometric method,[10] the method of Blank and Finkenbeiner and the ammonia method; while the potassium cyanide method he recommends only in the case of very dilute solutions such as are met with when determining formaldehyde in milk.[11] The impression, therefore, which one obtains from the literature on the subject as has been referred to, is that while the potassium cyanide method is admittedly a very good method for determining formaldehyde in dilute solutions it is not recommended in the case of the concentrated or moderately strong solutions, and that in such cases it is preferable to use one of the other methods, of which the hydrogen peroxide method is the most favored. An examination of the leading pharmacopœias as to the methods chosen for assaying commercial formaldehyde solutions also seems to confirm the conclusion that the potassium cyanide method is not generally regarded as a method suitable for use in such cases. Thus the U. S. Pharmacopœia (1905) adopts the hydrogen peroxide method, the German Pharmacopœia (1910) gives the acidimetric sodium sulphite method, the British Pharmaceutical Codex (1907) recommends the ammonium chloride and iodometric methods, while the French Pharmacopœia (1908) agrees with the U. S. Pharmacopœia in giving preference to the hydrogen peroxide method. Finally, we may mention that according to Fresenius and Grünhut[12] there really are only four methods in use for assaying commercial formaldehyde, namely, the ammonia method of Legler, the method in which the

[10] *Ibid.* It may be noted in this connection that both here and in the first edition (p. 665) there seems to be an error in some of the figures given. For if we take 10 c.c. of a 3 per cent. formaldehyde solution (it is directed that the solution is to be diluted "to a strength not exceeding 3 per cent.") we will be operating on about 0.3 Gm.; and since "two atoms of iodine are equivalent to one molecule of formaldehyde," 0.3 Gm. HCHO will require 200 c.c. of N/10 iodine, whereas according to the given directions only 25 c.c. of N/10 iodine are to be taken. The same error is found also in Leffmann and Beam: Food Analysis, 2d ed., p. 84 (1905).

[11] *Ibid.*, p. 181. There seems to be also an oversight in this connection, since it is directed to use ferric *chloride* as the indicator in titrating the excess of silver.

[12] *Zeit. anal. Chem.*, **44**, p. 13 (1905): "Doch sind es—soweit unsere Kenntnis reicht—im wesentlichen nur vier Verfahren, deren man sich in der Technik zur Betriebskontrolle, sowie zur Wertbestimmung des Handelsproduktes, bedient: die Ammoniak-Methode von Legler, die Oxydation mit Natronlauge in Druckflaschen, die Wasserstoffsuperoxyd-Methode von Blank und Finkenbeiner, und endlich die jodometrische Methode von Romijn."

formaldehyde is treated with sodium hydroxide in pressure bottles, the hydrogen peroxide method of Blank and Finkenbeiner, and the iodometric method of Romijn.

On the other hand, the meaning of the objection advanced by Smith against the use of the potassium cyanide method for determining formaldehyde in strong solutions, namely, "that in diluting strong solutions to the range of these methods, a small error in weighing may be considerably multiplied," is difficult to understand. For supposing that 1 Gm. of the formaldehyde solution is weighed out, diluted with distilled water to 100 c.c. and 25 c.c. of the resulting solution taken for the analysis, and supposing that the delicacy of the balance used is only ± 0.001 Gm., then the actual amount taken for the analysis would be 0.250 Gm. ± 0.00025 Gm., involving therefore a possible error of ± 0.1 per cent. Now if the step of diluting and taking for the analysis an aliquot portion were omitted and the total amount weighed out were used for the analysis, the amount so taken would be 1. ± 0.001 Gm., the possible error involved would therefore be exactly the same as before, namely, ± 0.1 per cent. It is possible that "error in weighing" is an oversight, the intention having been—error in *measuring*. If this was the intention, we can readily see how an error might be introduced through an error in measuring. For supposing that instead of using for the analysis the entire amount weighed out, it be diluted to a definite volume and 5 c.c. of this solution taken for the analysis. In measuring out the 5 c.c. there might be an error, say of ± 0.05 c.c. This would introduce an error of ± 1 per cent., which would have been avoided if the analysis had been carried out directly on the weighed amount of formaldehyde solution. But even in this case the error would not be "multiplied," unless more than one dilution be made. Moreover, if instead of using only 5 c.c. of the diluted solution a larger volume be taken, say 25 c.c., an equal absolute error in the measuring would, of course, relatively be only one-fifth, or reducing the possible error from ± 1 to ± 0.2 per cent. In other words, a procedure which would involve the dilution of a certain weight of the strong formaldehyde solution to 100 c.c. and the use of 25 c.c. of the diluted solution for the analysis, would ordinarily involve no greater error than the inherent errors of volumetric analysis. And since all the methods compared are volumetric, any such errors may be considered equally possible in all of them. For supposing that in measuring out the 25 c.c. of the diluted formalde-

hyde solution there might be an error of ± 0.05 c.c. or ± 0.2 per cent., might there not also be a similar error when the same measuring instrument will be used for measuring out the 25 c.c. of twice normal NaOH (according to Smith) in the case of the hydrogen peroxide method? Besides, in taking 25 c.c. of the 100 c.c. of the diluted formaldehyde solution it is not necessary that the measuring instrument used should measure out exactly 25 c.c. but only that the volume so measured out be one-fourth of the total, and whether this is the case can be readily and conveniently ascertained by using the same measuring instrument for filling the empty 100 c.c. flask with water and seeing whether four fillings will fill it exactly to the mark. This will prove the accuracy of the instrument for this purpose or enable the operator to apply the proper correction. It would seem therefore that if the potassium cyanide method is an excellent method for determining formaldehyde in dilute solutions it may be used with equal advantage in the case of strong solutions by suitably diluting the latter with water.

That such is really the case may be seen from Smith's own results. Using the potassium cyanide method for strong formaldehyde solutions, in which case "all solutions containing more than one per cent. were diluted," the three results given in the case of the 37 per cent. formaldehyde solution are: 37.12, 37.07, and 37.18 per cent. Likewise, the results of Williams, when using the potassium cyanide method for determining the formaldehyde in the concentrated solution, show that very concordant results are obtained by this method. Thus six determinations yielded the following percentages: 35.15, 35.06, 35.23, 35.01, 35.21, 35.07, or a maximum difference from the average (35.12) of only 0.11 per cent. When using the hydrogen peroxide method, four determinations yielded the following percentages: 35.82, 35.92, 35.74 and 35.78, or a maximum difference from the average (35.81) of 0.11 per cent. It is thus seen that the potassium cyanide method can be applied to strong formaldehyde solutions by suitably diluting them, the results thus obtained being equally concordant as those obtained by the hydrogen peroxide method. It therefore remains only to clear up the point as to whether or not the lower results obtained by the potassium cyanide method as compared with those obtained by the hydrogen peroxide method may be due to possible incompleteness of the reaction between the KCN and the formaldehyde.

If we will suppose that the reaction between the KCN and the

formaldehyde is not complete, we must assume that the value of $c_1p_1q_1$ in the general equation

$$V = v - v_1 = cpq - c_1p_1q_1,$$

which is the fundamental equation underlying all chemical dynamics,[13] is not negligible but has a value which would account for the lower results obtained by the KCN method. That is, in the reaction between the formaldehyde and the KCN, which may be represented by the equation

$$CH_2O + KCN \rightleftarrows N \equiv C-\underset{\underset{H}{|}}{\overset{\overset{H}{|}}{C}}-O-K$$

we must assume that the velocity of the reaction which tends to decompose the condensation product back into formaldehyde and KCN has an appreciable value. From the law of mass action it would follow, therefore, that if we were to vary the mass of one of the reacting substances the point at which equilibrium is established should also vary; just as in the classical instance of an incomplete reaction, namely, the reaction between acetic acid and ethyl alcohol, in which case Berthelot and Pean de Saint Gilles[14] found that by varying the amount of alcohol with respect to that of the acid the amount of ester produced also varied, being only 66.5 per cent. of the theory when one equivalent of alcohol was used but increasing to 82.8 per cent. when two equivalents of the alcohol were added. In order, therefore, to determine whether any such variation occurs in the case of the reaction between formaldehyde and KCN, the following experiments were carried out on mixtures of formaldehyde and KCN, in which the amount of KCN added varied from approximately one to three equivalents.

Mode of Procedure.

A formaldehyde solution was prepared by diluting 21.1879 Gms. of a sample of U.S.P. solution of formaldehyde to 2000 c.c. with distilled water. Portions of 15 c.c. of this solution were mixed at room-temperature (22–25° C.) with varying amounts of approximately N/10 KCN, the minimum amount of which was just a little in excess of that theoretically required to combine with all of the formaldehyde taken, while the maximum amount of KCN used was about two equivalents more than necessary for a complete equi-

[13] Jones: Elements of Physical Chemistry, 3rd ed., p. 529 (1907).
[14] *Ibid.* p. 522.

molecular union. The KCN solution was prepared from a sample of Kahlbaum's potassium cyanide, and its value in terms of tenth-normal silver nitrate was determined simultaneously with each series of experiments, the determination being carried out in a manner similar to that used for determining the uncombined cyanide in the experiments. The mixing of the formaldehyde and potassium cyanide solutions was generally effected in Erlenmeyer flasks; and immediately after mixing (the latter operation consuming about half a minute), the resulting solution was added to a mixture of a known amount of silver nitrate and nitric acid in a 200 c.c. measuring flask. The amount of silver nitrate used was sufficient in every case to combine with all of the excess of KCN and calculated to leave in the filtrate, for the subsequent titration, the equivalent of about 2 c.c. of N/10 KCNS per 100 c.c. of the filtrate. The amount of nitric acid used was 10 or 20 c.c. of U.S.P. dilute (10 per cent.) nitric acid. After thoroughly washing the Erlenmeyer flask in which the KCN and formaldehyde solutions were mixed and adding the washings to the flask containing the acidified silver nitrate solution, the whole was made up to 200 c.c. with distilled water, thoroughly shaken, filtered through a dry filter, and 100 c.c. of the filtrate titrated for the excess of silver by means of N/10 KCNS, using 2 c.c. of a 10 per cent. ferric alum solution as indicator. The results obtained are given in Table I.

TABLE I.

EFFECT OF VARYING THE EXCESS OF KCN.

No. of experiment	Amount of formaldehyde solution taken	Amount of N/10 KCN added [a]	Amount of N/10 $AgNO_3$ used	N/10 KCNS required for ½ of filtrate	Found equivalent of the formaldehyde solution in terms of N/10 $AgNO_3$
	(c.c.)	(c.c.)	(c.c.)	(c.c.)	(c.c.)
1	15	19.7	4	1.50	18.45
2	15	20.0	4	1.45	18.65
3	15	21.0	5	1.55	18.84
4	15	22.0	6	1.67	19.07
5	15	23.0	7	1.75	19.21
6	15	24.0	8	1.75	19.20
7	15	25.0	9	1.80	19.29
8	15	27.0	11	1.85	19.36
9	15	30.0	14	1.83	19.29
10	15	40.0	24	1.90	19.30
11	15	50.0	34	1.98	19.34
12	15	60.0	44	2.02	19.29

[a] The KCN solution was only approximately tenth-normal, 48 c.c. being equivalent to 47.4 c.c. N/10 $AgNO_3$.

The results given in Table I show that the maximum result was reached when the excess of KCN was about one-half of an equivalent (exp. 8), while further increasing the amount of KCN up to approximately three equivalents did not appreciably alter the result. The reaction may therefore be regarded as complete, at least for all practical purposes, when the excess of KCN is as much as one-half of an equivalent. On the other hand, when the excess of KCN is less than one-fourth of an equivalent (exps. 1–6), the reaction is incomplete; and when the amount of KCN added is only slightly in excess of that required to combine with all of the formaldehyde present, the result is about 3 or 4 per cent. too low (exps. 1–2). That the excess of KCN must be above a certain minimum in order to insure a complete reaction is not brought out either in the original paper of Romijn or those of Smith or Williams. In fact, none of the literature examined has any reference to this point; while from the statement of Romijn that the method is based on the property [15] of formaldehyde to *immediately* add itself to potassium cyanide and his unmodified general statement [16] that when the KCN is in excess so much of the KCN becomes combined as to correspond to one molecule of KCN for every molecule of formaldehyde, one might suppose that the relative amount of the excess of KCN to be added does not matter. This conclusion would gain further support from the statement of Smith [17] that the determination is carried out by mixing the formaldehyde "with a known quantity of potassium cyanide, the latter being in excess."

In order to determine the effect of varying the time or the temperature, two series of experiments were carried out. In one of these, the mixtures of formaldehyde and KCN were allowed to stand for different intervals of time at the constant temperature of 15° C. and the residual cyanide then determined in the usual way. In the other, the time was constant but the temperature was made to vary between 5° C. and 40° C. In those cases where the mixtures had to stand for a considerable length of time, the flasks containing same were tightly stoppered by means of glass or rubber

[15] *Zeit. anal. Chem.*, **36**, 18 (1897): "die Eigenschaft des Formaldehyds, das Cyankalium sofort zu addiren."

[16] *Ibid.*: "wenn ein Ueberschuss von Cyankalium vorhanden war, wird von dem Cyankalium so viel gebunden, dass auf ein Molecül Formaldehyd ein Molecül Cyankalium kommt."

[17] *Jour. Amer. Chem. Soc.*, **25**, 1032 (1903).

stoppers and the value of the KCN solution was controlled by letting it stand under similar conditions and determining its strength at the end of the experiment. The experiments designed to show the effect of temperature were carried out as follows: The formaldehyde solution was placed in one Erlenmeyer flask while the KCN solution which was to be added to it was placed in another similar flask and both were then warmed or cooled to the desired temperature by being set in a large water-bath which was kept about a degree above or below the desired temperature, respectively. The time thus consumed was about half an hour. The KCN solution was then poured into the flask containing the formaldehyde solution and the mixture quickly transferred back again into the flask which contained the KCN solution and mixed in the usual way while the flask containing the solutions was still immersed in the water-bath. This mixture was then quickly poured into a mixture of silver nitrate [18] and nitric acid, in a 200 c.c. measuring flask, and mixed with it. Both flasks were then thoroughly washed with distilled water, the washings added to the silver solution, and the whole made

TABLE II.

EFFECT OF VARYING THE TIME.

Temperature: 15° c.

No. of experiment	Time mixture stood before added to silver solution	Amount of formaldehyde solution taken	Amount of N/10 KCN added [b]	Amount of N/10 $AgNO_3$ used	N/10 KCNS required for ½ of filtrate	Found equivalent of the formaldehyde solution in terms of N/10 $AgNO_3$
	Hours	(c.c.)	(c.c.)	(c.c.)	(c.c.)	(c.c.)
1	0*	25	33	5	1.80	31.33
2	0*	25	40	12	2.30	32.27
3	0*	25	48	20	2.38	32.36
4	1	25	33	5	1.80	31.33
5	1	25	40	12	2.30	32.27
6	1	25	48	20	2.40	32.40
7	18	25	33	5	1.82	31.37
8	18	25	40	12	2.25	32.17
9	18	25	48	20	2.35	32.30
10	42	25	33	5	1.85	31.43
11	42	25	40	12	2.30	32.27
12	42	25	48	20	2.35	32.30

*Added immediately after mixing.

[b] 48 c. c. of the KCN sol. was found equivalent to 47.6 c. c. N/10 $AgNO_3$.

[18] The amount of $AgNO_3$ varied as shown in the tables, while the amount of HNO_3 was the same in all cases, namely, 20 c.c. of 10 per cent. nitric acid.

up to 200 c.c. From this point the procedure was the same as that already described. Each of the different conditions of time and temperature was studied with three different KCN excesses, namely, a KCN excess of approximately one-hundredth, one-fourth, and one-half of an equivalent, respectively. The results obtained are given in Tables II and III.

TABLE III

EFFECT OF VARYING THE TEMPERATURE

No. of experiment	Amount of formaldehyde solution taken	Amount of N/10 KCN added [c]	Amount of N/10 $AgNO_3$ used	N/10 KCNS required for ½ of filtrate	Found equivalent of the formaldehyde solution in terms of N/10 $AgNO_3$
		Temperature: 5°C.			
	(c.c.)	(c.c.)	(c.c.)	(c.c.)	(c.c.)
1	25	33	5	1.90	31.50
2	25	40	12	2.30	32.23
3	25	48	20	2.38	32.32
		Temperature: 15°C.			
4	25	33	15	1.83	31.32
5	25	40	12	2.30	32.18
6	25	48	20	2.40	32.30
		Temperature: 30°C.			
7	25	33	5	1.60	30.86
8	25	40	12	2.20	31.98
9	25	48	20	2.40	32.30
		Temperature: 40°C.			
10	25	33	5	1.35	30.36
11	25	40	12	2.15	31.88
12	25	48	20	2.30	32.10

[c] 48 c.c. of the KCN solution was equivalent to 47.56 c.c. N/10 $AgNO_3$ in exps. 1–3; to 47.5 c.c. N/10 $AgNO_3$ in exps. 4–12.

From the results given in Table II it is seen that when the mixture of KCN and formaldehyde is allowed to stand 42 hours the result obtained is practically the same as when the mixture is immediately added to the silver solution. From the results given in Table III it is seen, however, that a variation in the temperature does have an appreciable effect on the results obtained, especially when the KCN added is only slightly in excess of that required to combine with all of the formaldehyde present. That this is so may also be seen from the following experiments: To each of four Erlenmeyer flasks there were added 25 c.c. of a dilute formaldehyde solution and 33 c.c.

of an approximately N/10 KCN solution and the flasks tightly stoppered by means of rubber stoppers. From the known value of the formaldehyde and KCN solutions [19] the amount of KCN added was calculated to be approximately one-hundredth of an equivalent in excess of that required to combine with all of the formaldehyde present. All these flasks were then set in a large water-bath, the temperature of which was kept at about 40° C., and allowed to remain in this bath for half an hour. At the end of this time, the contents of flask No. 1 was added to a mixture of 5 c.c. N/10 $AgNO_3$ and 20 c.c. of 10 per cent. nitric acid in a 200 c.c. measuring flask and the analysis completed as in the former experiments; while flasks Nos. 2, 3, and 4 were taken out of this bath and set in another large water-bath, which was kept at about 5° C. After remaining in this bath for half an hour, No. 2 was treated as No. 1 while Nos. 3 and 4 were taken out and placed again in the bath at 40° C. After this second warming to 40° C. No. 3 was treated as were Nos. 1 and 2, while No. 4 was taken out of this bath and set again in the bath at 5° C. After this second cooling to 5° C., No. 4 was treated as those preceding it. On titrating half of the final filtrate with N/10 KCNS, the following results were obtained:

							Found equivalent of the 25 c.c. formaldehyde solution in c.c. of N/10 $AgNO_3$
No. 1	required	1.45	c.c.	N/10	KCNS,	corresponding to	30.59
No. 2	"	2.03	"	"	"	"	31.75
No. 3	"	1.48	"	"	"	"	30.65
No. 4	"	2.01	"	"	"	"	31.71

On now repeating these experiments in exactly the same way except that the excess of KCN was increased [20] to approximately one-half of an equivalent (using 48 c.c. of N/10 KCN, whose factor was 0.9875), the following results were obtained:

							Found equivalent of the 25 c.c. formaldehyde solution in c.c. of N/10 $AgNO_3$
No. 1	required	2.42	c.c.	N/10	KCNS,	corresponding to	32.24
No. 2	"	2.50	"	"	"	"	32.40
No. 3	"	2.35	"	"	"	"	32.10
No. 4	"	2.50	"	"	"	"	32.40

[19] 25 c.c. of the formaldehyde solution used were found equivalent to 32.4 c.c. N/10 $AgNO_3$, while 33 c.c. of the KCN solution were found equivalent to 32.69 c.c. N/10 $AgNO_3$.

[20] The amount of N/10 $AgNO_3$ used was also increased to 20 c.c.

These results, therefore, like the results given in Table III, show that when only a comparatively small excess of the KCN is used, the effect of a considerable variation in the temperature manifests itself quite markedly in the results; but when the excess of KCN is increased to about one-half of an equivalent, the results obtained at 40° C. are only slightly lower than those obtained at 5° C.; while the results given in Table III show that a variation of the temperature between 5° C. and 30° C. had no appreciable effect on the found value of the formaldehyde solution when the excess of KCN was about one-half of an equivalent. We may conclude, therefore, that the ordinary changes in room-temperature during the year will not appreciably affect the results when the excess of KCN is as much as one-half of an equivalent.

A closer examination of the potassium cyanide method seemed to show also that there is nothing inherent in the basic principle of this method which would prevent its application directly to the concentrated formaldehyde solutions. That such is really the case may be seen from the following experiment: To 0.5505 Gm. of a sample of U.S.P. formaldehyde, weighed out in a closely fitting glass-stoppered Erlenmeyer flask of about 150 c.c. capacity, there were added 100 c.c. of an approximately N/10 KCN solution [21] and the two solutions well mixed. This mixture was then added to a mixture of 35 c.c. N/10 $AgNO_3$ and 20 c.c. 10 per cent. nitric acid in a 200 c.c. measuring flask, the Erlenmeyer well washed and the washings added to the silver solution, the whole made up to 200 c.c., thoroughly shaken, and filtered through a dry filter. 100 c.c. of this filtrate were found to require 2.00 c.c. N/10 KCNS. This would make the formaldehyde in the 0.5505 Gm. of the sample equivalent to 67.75 c.c. N/10 $AgNO_3$ which would correspond to 0.20325 Gm. HCHO or 36.92 per cent. On analyzing a diluted solution of this sample, the result obtained corresponded to 36.98 per cent. It is thus seen that not only is the potassium cyanide method applicable to concentrated formaldehyde solutions by previously diluting them with water but that it may even be applied to the concentrated solution directly, just as in the case of the hydrogen peroxide method.

It has already been pointed out above that in the case of the concentrated formaldehyde solution the H_2O_2 method seems to

[21] 48 c.c. of this KCN solution was equivalent to 47.4 c.c. N/10 $AgNO_3$.

be the most generally favored and that it is the official method of the present U. S. Pharmacopœia. We may therefore ask, What advantages has the H_2O_2 method over other methods, such as the iodometric or Legler method, which entitle it to this preference? The answer to this may be found partly in the results of Williams [22] who found that in the presence of small amounts of ethyl alcohol, paraldehyde, methyl alcohol, or acetone, the H_2O_2 method gave normal results whereas the results obtained by the iodometric method were abnormal. Similarly, in the case of a formaldehyde solution which contained a small amount of acetaldehyde, the result obtained by the Legler method was 47.8 per cent. instead of 34.87 per cent. in the absence of the acetaldehyde, thus increasing the result in percentage by 12.93; whereas by the H_2O_2 method, under similar conditions, the increase in the percentage was only 2.78 (from 35.82 to 38.6). The results of Williams, however, while showing that the H_2O_2 method is more advantageous than the iodometric or Legler methods, also show that the KCN method is even more reliable than the H_2O_2 method. For not only were the results by the KCN method normal in all cases where the H_2O_2 method gave normal results but even in the presence of acetaldehyde which, as already noted, increased the results by the H_2O_2 method from 35.82 to 38.6 per cent., the result obtained by the KCN method was only slightly higher than in the absence of the acetaldehyde, being 35.12 per cent. in the absence of the acetaldehyde and 35.3 per cent. in its presence; while according to Romijn [23] very exact formaldehyde determinations may be obtained by the KCN method even in the presence of acetaldehyde, acetone or benzaldehyde. We thus see that not only has the KCN method the advantage over the H_2O_2 method in that the reaction on which the former method is based is characteristic for aldehyde but that it may even be used for distinguishing and determining formaldehyde in the presence of certain other aldehydes. The fact also that in the H_2O_2 method the results will be influenced by any substance which on oxidation, under the conditions of the method, will produce acid products capable of consuming a portion of the alkali present, has led Fresenius and

[22] *Jour. Amer. Chem. Soc.*, 600 (1905).

[23] *Zeit. anal. Chem.*, **23**, 22 (1897): "Die Cyankaliummethode gestattet also auch bei Anwesenheit von Acetaldehyd, beziehungsweise Aceton oder Benzaldehyd, eine sehr genaue Bestimmung des Formaldehyds."

Grünhut [24] to recommend that in assaying commercial formaldehyde by the H_2O_2 method the results obtained should be confirmed by the iodometric method, since it is only when both methods give closely agreeing results that the mean of the two may be taken to represent the actual amount of formaldehyde in the solution.

But these are not the only disadvantages of the H_2O_2 method. For according to Smith,[25] the "working range" of the H_2O_2 method, on the lower end, ends with solutions containing about 5 per cent. HCHO; so that when we have occasion to carry out comparative experiments requiring a knowledge of the formaldehyde content of the strong solutions and also of solutions which contain considerably less than about 5 per cent. formaldehyde, if we would use the H_2O_2 method we would be obliged to use two different methods in the same work. Therefore, should we not prefer a method (the KCN method) which can be universally applied to formaldehyde solutions, whether these be strong or weak with reference to their formaldehyde content, and which is based on a reaction that is characteristic of aldehyde and also permits of distinguishing and estimating formaldehyde in the presence of certain other aldehydes? Finally, we may add that the KCN method has also the advantage of being based ultimately on the beautiful and exact Volhard thiocyanate method and that the silver nitrate solution required comes nearest to the chosen ultimate standard for volumetric solutions—pure metallic silver.[26]

In connection with the study of embalming fluids to which reference has already been made above, it was desired also to obtain

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[24] *Zeit. anal. Chem.*, **44**, 15–16 (1905): "Wir sind immer dafür eingetreten, diese beiden Arbeitsweisen bei der Handelsanalyse, insbesondere bei der Schiedsanalyse, neben einander zu benutzen und das Mittel der nach beiden Verfahren erhaltenen und hinreichend übereinstimmenden Werte als den wahren Formaldehyd gehalt anzusehen. Diese Forderung, zwei verschiedene Methoden anzuwenden, beruht darauf, dass beide nicht eigentlich auf die directe Bestimmung des Formaldehyds abzielen, ihn also nicht in einer wohlcharacterisierten und leicht zu identifizierenden Verbindungsform abscheiden. Beide benutzen viel mehr Reactionen, die ausser dem Formaldehyd noch sehr viele andere Verbindungen zeigen können: die eine lässt alle Substanzen finden, die in alkalischer Lösung durch Wasserstoffsuperoxyd zu Säuren oxydiert werden, die andere alle die jenigen, die in alkalischer Lösung durch Jod oxydiert werden oder in anderer Weise Jod verbrauchen, ohne es beim Ansäuren wieder frei zu geben."

[25] *Jour. Amer. Chem. Soc.*, **25**, 1034 (1903).

[26] Elvove: AMER. JOUR. PHARM., **82**, 203–211 (1910)

an idea as to degree of variation in the strength of the commercial formaldehyde on the American market. Accordingly, samples were obtained from the principal American firms who sell this article. And inasmuch as, for the reasons given above, the KCN method may be considered as more reliable for determining the actual formaldehyde content of such solutions, the determinations were carried out by this method. Seven samples were examined. The results obtained are given in Table IV.

TABLE IV.

SHOWING THE HCHO STRENGTH OF VARIOUS SAMPLES OF COMMERCIAL FORMALDEHYDE.

No. of sample	Amount of formaldehyde[d] solution taken (c. c.)	Amount of N/10 KCN added[e] (c. c.)	Amount of N/10 $AgNO_3$ used (c. c.)	N/10 KCNS required for ½ of filtrate (c. c.)	Found equivalent of the formaldehyde solution in terms of N/10 $AgNO_3$ (c. c.)	Amount of HCHO expressed in percentage by weight (Per cent.)
1	25	48	20	1.75	31.10	35.47
2	25	48	20	2.05	31.74	36.11
3	25	48	20	2.00	31.64	36.21
4	25	48	20	2.30	32.25	36.53
5	25	48	20	2.35	32.34	36.61
6	25	48	20	2.40	32.44	36.98
7	25	48	20	2.91	33.46	37.97

[d] These solutions of formaldehyde contained the following amounts in grams of the respective samples of the concentrated formaldehyde in 2000 c. c.: No. 1, 21.0418; No. 2, 21.0958; No. 3, 20.9690; No. 4, 21.1879; No. 5, 21.2005; No. 6, 21.0512; No. 7, 21.1459.

[e] The found value of the KCN solution was as follows: In the case of No. 1, 48 c. c. was equivalent to 47.6 c. c. N/10 $AgNO_3$; in No. 4, to 47.65; and in the remainder, to 47.64 c. c. N/10 $AgNO_3$.

The results given in Table IV show that the majority of the samples examined contained slightly less formaldehyde than is required by the present U.S.P. ("not less than 37 per cent. by weight"), and that only two (Nos. 6 and 7) of the seven samples examined may be said to have come up to its requirement. Similar results have also been obtained by Evans Sons Lescher and Webb,[27] who found that the nine samples of commercial formaldehyde solution which they examined ranged from 37 down to 35.4 per cent.

[27] Evans Sons Lescher and Webb: Analytical Notes, 1907, 1908, p. 22.

of absolute formaldehyde by weight. Likewise, Bachman [28] reports solution of formaldehyde ranging from 36.6 per cent. to 31.8 per cent., instead of the minimum of 37 per cent. as required by the present U.S.P. Finally, we may mention in this connection that the formaldehyde requirement of the French Pharmacopœia (1908) and also of the German Pharmacopœia (1910) is only 35 per cent. by weight of absolute formaldehyde. On the other hand, with the exception of only one sample (No. 1), all contained more than 36 per cent. by weight of absolute formaldehyde. Therefore, bearing in mind the comparative difficulty of manufacturing and keeping unaltered solutions of formaldehyde of considerably higher concentration than the minimum of the present U.S.P.; and also that by making the U.S.P. requirement more in harmony with these latter pharmacopœias and with what seems to be the actual condition of the American market, it would not mean that the purity requirement will be lowered but only that the solution will be just a little less concentrated; it would seem advisable that the formaldehyde requirement, in the next revision of the U.S.P., be changed from the present minimum of 37 per cent. to a minimum of 36 per cent. by weight of absolute formaldehyde. Also that the KCN method might with advantage be substituted for the present H_2O_2 method. The KCN method, applied to U.S.P. solution of formaldehyde, may be carried out as follows:

Transfer 0.5 c.c. of the sample of Solution of Formaldehyde to a well-stoppered Erlenmeyer flask of about 150 c.c. capacity and determine its weight. Add to it immediately 100 c.c. of a solution of potassium cyanide of a strength close to tenth-normal (6.5 Gm. KCN to 1000 c.c.), the exact strength of which is known. Mix well, and add to a mixture of 40 c.c. N/10 silver nitrate and 10 c.c. of dilute (10 per cent.) nitric acid, in a 200 c.c. measuring flask. Wash the Erlenmeyer flask, adding the washings to the silver solution, and make up the whole to 200 c.c. Shake thoroughly, filter through a dry filter, and titrate the excess of silver in 100 c.c. of the filtrate by means of N/10 ammonium or potassium sulphocyanate, using ferric alum as indicator. The number of c.c. of N/10 sulphocyanate found to require, multiplied by 2, and the product subtracted from 40, will give the equivalent of the uncombined KCN in c.c. of

[28] Proc. Minnesota Pharm. Ass., 1907, p. 41; from Bull. No. 63, Hyg. Lab., U. S. Pub. Health & Mar. Hosp. Serv., Wash., p. 295.

N/10 $AgNO_3$. Subtracting this from the corresponding equivalent of the total KCN added, multiplying the difference by 0.3, and dividing this product by the weight of the sample taken, the quotient will represent the percentage by weight of absolute formaldehyde in the sample.

TINCTURE OF CANTHARIDES.[1]

By E. G. Eberhardt, Indianapolis, Ind.

About two years ago when an attempt was made to prepare a standardized fluid extract of cantharides, it was discovered that such a preparation was an impossibility because of the sparing solubility of cantharidin in alcohol, the latter being considered the only proper solvent. When the investigation was extended to the tincture it was found that, for the same reason, a tincture could not be made which represented 10 per cent. of drug. The latter, if of good quality, will average about 1 per cent. of cantharidin, but the tincture made by the official method only assays from 0.03 per cent. to 0.04 per cent. This same fact was brought out in a paper on "Tincture Cantharides," by Prof. W. L. Scoville, read at the 1910 meeting of the American Pharmaceutical Association and he there recommends a menstruum of alcohol 15 volumes and glacial acetic acid 1 volume as giving a much better tincture, the results averaging from 0.057 per cent. to 0.064 per cent. Prof. Scoville also determined the solubility of cantharidin in official alcohol at 25° C. to be 1 : 1333 (W.V.). Accordingly it would be possible to have a tincture made with alcohol assaying .075 per cent. unless the accompanying extractive would decrease the solvent power of the menstruum for cantharidin.

As complete extraction of cantharides could not be accomplished with alcohol at the ordinary temperature an attempt was made to obtain an alcoholic preparation of maximum strength by the use of heat. A lot of tincture was made by digesting the drug in a closed vessel with hot alcohol for about two hours, allowing to cool at room temperature, draining off the liquid, digesting the residue with a fresh portion of alcohol and washing the residue finally with sufficient alcohol to make the required amount. This

[1] Presented before the Division of Pharmaceutical Chemistry at the Indianapolis meeting of the American Chemical Society, July, 1911.

tincture assayed 0.031. Hot percolation was employed on another lot, stopping when the correct amount of tincture was obtained. This assayed 0.035. The drug was thereupon further percolated, the weak percolate reduced to small volume under reduced pressure and incorporated with the first percolate which then assayed 0.0499. The small amount of light-colored sediment which forms in these tinctures, on standing, contains cantharidin which may be ammonium cantharidate or some similar combination, as it is quite likely that ammonia or an amine is formed when the drug is subjected to heat or by aging. A small experimental lot was now made, using hot percolation and obtaining four successive fractions each equal in volume to the amount of tincture to be finished. These assayed as follows:

No. 1—.058	No. 3—.003
No. 2—.010	No. 4—.002

It is evident that the first two fractions contain practically all the cantharidin that can be obtained in this way. This, however, is only about two-thirds of what was in the drug and the question arises, why were the succeeding fractions so weak? The solution probably lies in the condition indicated above, that part of the cantharidin is present as a cantharidate which is but very sparingly soluble in alcohol. From this, it seems imperative that some acid be used if alcohol is to be the extracting agent or if, as later results show to be desirable, the cantharidin is wanted in the uncombined state. However, a better solvent than alcohol is needed to make a full-strength tincture even though acid is used. This is shown by the fact that when the drug was moistened with a mixture of equal parts glacial acetic acid and alcohol, allowed to stand several hours and then percolated with alcohol, the resulting tincture assayed only .04.

The plan of converting all the cantharidin into cantharidate was next tried and a portion of drug was mixed with magnesium oxide, moistened with water and dried at a gentle heat. It was then divided, one-half being percolated with alcohol and the other half with dilute alcohol. The resulting tinctures assayed: alcohol .023 and dilute alcohol 0.053, showing that the weaker menstruum is much the better for combined cantharidin. Using a caustic alkali, it was found necessary to add considerable excess as the fat present in the drug requires a certain amount for saponification. A quantity of drug was moistened with one-tenth its weight of caustic

potash dissolved in water, the magma heated on the water-bath to complete the reaction and, as it was in no condition to percolate, it was dried at a gentle heat and ground. It could then be percolated with dilute alcohol and yielded a tincture assaying 0.106, which practically represented the full strength of the drug.

This tincture was compared for vesicating power with a U.S.P. tincture assaying about one-third as much cantharidin. Three drops of the U.S.P. tincture caused distinct redness on a man's arm and six drops produced vesication. Three drops of the alkaline tincture produced no visible effect and six drops only a slight redness. When equal volumes were evaporated spontaneously, a few drops of acetic acid added to each, and then mixed with a definite amount of lead plaster, the effects were about equal when applied to a shaven area on a dog's leg, each producing redness in five hours, and vesicles in 15 hours. As the presence of lead plaster may have prevented to a considerable extent the liberation of cantharidin, this test was repeated, using lanolin as a base. The result did not materially differ from that previously obtained even when the test was repeated with a larger amount of acetic acid. When the tincture itself was acidified and filtered it assayed only .062, showing a loss of 40 per cent. of cantharidin which in all probability would be still greater on longer standing. As acetone is a much better solvent for cantharidin than alcohol a tincture was made by exhausting the drug with acetone, recovering the solvent and dissolving the residue in alcohol. This tincture assayed 0.066 and probably contained all the free cantharidin in the drug. It is a question, however, whether this amount of cantharidin would remain permanently in solution in an alcoholic tincture and as there can be no serious objection to the use of acetone as a menstruum, a final experiment was made in which the cantharides was moistened with a mixture of acetone 19 parts and glacial acetic acid 1 part, and then percolated with acetone. When one-half the required amount of tincture had been obtained, the percolate was almost colorless and therefore this first half was assayed separately from the second half. A second fraction equal in volume to the finished tincture was also obtained and assayed. The results were as follows:

1st half of tincture = 0.140
2d half of tincture = 0.0078 } average = 0.0739
Fraction No. 2 = 0.01

The finished tincture, that is the mixture of the two halves, was found to be more actively vesicant than the U.S.P. tincture.

It is probable that the acid added to the first part of the menstruum was insufficient in amount, or that, for some other reason, some of the combined cantharidin failed to be liberated. This point should have further investigation. But it is very evident from the way in which extraction proceeded that acetone is a much better solvent for extracting cantharides than alcohol, and if used there would be practically no difficulty in making a full strength tincture. Some suitable acid should, however, be added to that part of the menstruum used for moistening and macerating the drug in such proportion as to insure the liberation of all combined cantharidin.

To summarize, cantharides can be exhausted by gently heating with a solution of a caustic alkali to convert the cantharidin into cantharidate, drying, grinding and extracting with dilute alcohol. The resulting preparation, however, is weak in vesicating power. Exhaustion can also be accomplished by liberating any combined cantharidin present in the drug by means of a suitable acid and then extracting with acetone. The resulting preparation is actively vesicant.

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THE ASH CONTENT OF DRUGS.[1]

BY M. I. WILBERT, Washington, D. C.

In recent years there has been evidenced a growing disposition to place considerable reliance on the ash content of drugs as an aid in determining the nature and purity of the product under examination.

With a view of ascertaining what if any uniformity exists in the permissible ash content of official drugs, an analysis of the requirements made in ten of the recently published pharmacopœias was made and the maximum ash content of some of the more widely used drugs is herewith presented in the form of a table.

Restricting the permissible quantity of ash in connection with vegetable or crude drugs is a comparatively modern requirement. It was introduced in the second edition of the German Pharmacopœia,

[1] Read at the Boston meeting of the American Pharmaceutical Association, August, 1911.

published in 1882, and also appears in connection with a limited number of the drugs described in the U.S.P. of the same period. The number of official limitations for ash was increased but slowly and in the German Pharmacopœia for 1900 we find but 12 while in the corresponding U.S.P. VIII there are 15 such requirements in connection with the monographs for crude drugs.

The Netherlands Pharmacopœia published in 1905 appears to have been the first of the more widely known pharmacopœias to include an appreciable number of ash determinations, a total of 41.

In the Ph. Austr. VIII, published in 1906, this number is increased to 147, the maximum up to the present time, though the aggregate of the Ph. Helv. IV is nearly if not quite as great.

The Ph. Svec. IX, published in 1908, contains but a comparatively few definite figures, and the Ph. Hung. III, published in 1909, despite the fact that it follows the Austrian Pharmacopœia in many of the official requirements includes but a limited number of limitations for ash.

The German Pharmacopœia, which for some decades appears to have served as a model for the elaboration of our own U.S.P., has been continued within conservative lines and the new D.A.B.V. published in 1910 contains but a total of 34 requirements for ash content.

The impracticability of deducing any definite generalizations from the permissible limitations for ash included in the several pharmacopœias is well illustrated by the appended table. For many of the drugs the figures vary from 10 to 100 per cent. and in the limited number of cases where there is little or no variation, lupulin, for instance, the figures given have been found to be altogether too low for the commercially available product.

The variation in the actual ash content of drugs necessarily depends on many factors that are entirely beyond the control of the pharmacist or the dealer in drugs, but the frequently observed variation in the ash content of the same sample or lot of a drug is due to causes that are deserving of careful consideration on the part of the revisers of the Pharmacopœia. The fundamentally important factors for securing uniformity are to be sought in the method of incineration and the method of sampling employed therewith.

In the routine work of the ordinary analytical laboratory it is impracticable to incinerate more than 1 or 2 Gms. of a sample of crude drug, and it is quite apparent that it would be difficult indeed

to secure a representative sample of a root, bark, leaf or herb that could be relied upon without resorting to comminution and subsequent mixing of an appreciable quantity of the drug.

This difficulty of securing representative samples of many crude drugs has no doubt deterred the revisers of some of the more recent pharmacopœias from adopting the ash content factor more freely.

It is generally agreed that the exact method for determining the residual ash should be described so as to obviate, if possible, the likelihood of the residue retaining an undue amount of unconsumed carbon.

The Ph. Austr. VIII, despite the fact that it includes upwards of 150 limitations for the ash content of drugs, does not provide a method for determining this rather important requirement, and the several critics of this Pharmacopœia have not failed to assert that the commission in charge of the revision adopted theoretic rather than practical standards for many of the pharmacopœial drugs.

The Ph. Helv. IV directs that ash determinations are to be made by heating from 1 to 2 Gms. of the substance at first moderately, with a low flame, and then gradually increasing the temperature until the residual ash is free from carbon.

The nature of the container in which the substance is to be incinerated is not specified and no provisions are made for aiding the combustion of protected carbon particles.

The new German Pharmacopœia process is much more complete. It directs that a suitable quantity of the substance is to be incinerated in a recently heated and tared crucible, and in the event that complete combustion of the carbon particles is not brought about by continued moderate heating the material is to be leached out with hot water and the residual carbon again heated as before. The resulting solution is subsequently evaporated and the weight of the dry residue is added to that of the ash.

This Ph. Germ. V method has been liberally criticised, many pharmacists believing that the leaching out method is much more time-consuming than the methods which involve the use of clean sand for distributing the particles of carbon and the use of oxygen carriers such as nitric and oxalic acids for facilitating combustion.

Considerable difference of opinion appears to exist regarding the desirability of determining the ash, and other analytical factors, on the air-dried drug or on the drug dried to constant weight in an exsiccator.

In view of the fact that it is the air-dry drug that appears in commerce and is generally used in the making of galenical preparations as well as dispensing it would appear preferable to base pharmacopœial requirements on the commercial drug and to add such other restrictions as may be found necessary to limit the percentage of contained moisture.

TABLE SHOWING THE MAXIMUM ASH CONTENT OF SOME WELL KNOWN DRUGS INCLUDED IN 10 OF THE RECENTLY PUBLISHED PHARMACOPŒIAS.

Title of Drug.	Ph. Germ. V.	Ph. Hung. III.	Ph. Ital. III.	Ph. Fr. V.	Ph. Svec. IX.	Ph. Helv. IV.	Ph. Aust. VIII.	Ph. Belg. III.	Ph. Ndl. IV.	U. S. P. VIII.
Acacia	5.0	5.0	4.0	...	5.0	4.0	3.0	5.0	4.0	4.0
Adeps lanæ	0.1	0.05	...	...	...	...	...	0.05	0.10	0.30
Aloe	1.5	...	2.0	1.5	...	1.0	1.0	...	1.5	...
Althaea	...	...	...	...	...	6.0	6.0	7.5	7.0	...
Amylum	1.0	0.5	1.0	1.0	...	0.5	0.5	1.0	1.0	...
Anisum	10.0	...	...	...	...	10.0	10.0	12.0	...	...
Asafœtida	15.0	...	10.0	10.0	10.0	20.0	10.0	10.0	10.0	15.0
Belladonna folia	15.0	...	...	...	...	15.0	15.0	...	...	...
Benzoimum	2.0	...	2.0	2.0	...	1.5	2.0	...	2.0	2.0
Calumba	...	...	...	...	...	8.0	6.0	...	...	...
Cantharis	8.0	...	7.0	...	...	8.0	8.0	...	9.0	8.0
Capsicum	6.5	5.0	...	...	...	6.5	6.5	...	...	...
Carbo ligni	5.0	...	2.0	...	...	2.0	...	...	2.0	...
Cardamomum	...	...	...	...	...	10.0	8.0	...	8.0	4.0
Carum	8.0	...	...	...	...	8.0	7.0	...	...	8.0
Caryphyllus	8.0	...	...	...	...	7.0	8.0	...	6.0	8.0
Cinchona	...	...	6.0	...	...	6.0	6.0	...	8.0	...
Cinnamomum zeylanicum	5.0	...	...	...	...	5.0	5.0	7.0	8.0	4.0
Coccus	...	...	...	...	...	6.0	...	...	...	6.0
Cubeba	8.0	...	9.0	...	...	8.0	9.0	...	10.0	...
Digitalis	...	...	...	...	...	10.0	10.0	12.0	...	...
Ergota	...	...	5.0	...	...	5.0	5.0	...	5.0	...
Fœniculum	10.0	...	...	...	...	10.0	10.0	12.0	...	...
Gelatina	2.0	...	2.0	2.0	...	2.0	2.0	2.0	3.0	...
Gentiana	...	...	...	...	...	6.0	5.0	7.0	6.0	...
Glycyrrhiza	...	...	...	...	...	6.0	6.0	7.5	6.0	...
Gossypium purificatum	0.3	...	0.3	0.4	...	0.5	0.5	0.3	0.3	0.3
Granatum	...	...	...	...	...	15.5	10.0	...	15.0	...
Hydrastis	...	...	6.0	...	...	6.0	6.0	...	6.0	...
Hyoscyamus	24.0	...	...	...	...	...	...	...	...	...
Ipecacuanha	...	...	4.0	...	...	4.0	5.0	...	6.0	...
Jalapa	6.5	...	4.5	...	...	6.5	5.0	...	...	...
Linum	5.0	...	6.0	...	...	5.0	5.0	...	...	...
Lupulinum	...	...	10.0	...	...	10.0	10.0	...	...	10.0
Lycopodium	3.0	...	4.0	...	...	3.0	3.0	4.0	5.0	5.0
Manna	3.0	...	3.5	...	4.0	3.0	4.0	...	...	...
Mel	0.8	...	0.4	...	0.5	0.8	0.4	0.5	...	0.3
Myrrha	7.0	...	6.0	...	6.0	6.0	6.0	6.0	5.0	...
Nux vomica	3.0	...	...	...	...	3.5	3.0	...	...	...
Opium	...	...	6.0	...	...	5.0	6.0	...	...	...
Rhamnus purshiana	6.0	...	...	...	...	...	...	...	10.0	...
Rheum	12.0	...	12.0	...	...	13.0	12.0	...	12.0	...
Saccharum	0.1	...	...	0.075	...	...	...	...	0.1	...
Saccharum lactis	0.25	...	...	...	...	0.2	...	...	0.1	0.25
Scilla	5.0	...	...	...	...	5.0	8.0	...	...	...
Senna	12.0	...	...	...	...	12.0	10.0	12.0	8.0	...
Sinapis	...	...	5.0	...	...	5.0	5.0	5.0	8.0	...
Stramonium	20.0	...	...	...	...	...	...	...	...	...
Valeriana	...	...	...	...	...	12.0	10.0	15.0	...	...
Zingiber	7.0	...	...	...	...	7.0	5.0	...	8.0	...

This is apparently the view taken by the revisers of the German Pharmacopœia as that authority now requires that the official tests are to be applied to the air-dried substances unless otherwise directed.

From the available evidence it would appear that the determination of the ash content of official drugs is practicable and important in connection with non-structural drugs, like gums and resins, pollen grains, seeds, spices and powdered drugs generally.

It is not generally applicable to leaf drugs, barks or roots in the uncomminuted form because of the difficulty of sampling.

To insure correlating results the method to be employed must be described, and, other things being equal, this method should be one that can be easily followed by retail druggists ordinarily well equipped for work of this kind.

EXPERIMENTS WITH THE CAT METHOD FOR TESTING DIGITALIS AND ITS ALLIES.

By C. R. Eckler.

There are at present four American methods in use for the physiological testing of the digitalis series, namely: The twelve-hour frog method, proposed by Houghton; the one-hour frog heart method, proposed by Famulener and Lyons; the guinea pig method, proposed by Reed and Vanderkleed; and the cat method, proposed by Hatcher and Brody.

In view of the large amount of work which is being carried out just now with these methods, with the hope that some one may be found sufficiently accurate and convenient to justify its insertion into the next Pharmacopœia, it seemed proper to report some results obtained with one of these—the cat method of Hatcher and Brody. They describe their method in the American Journal of Pharmacy for August, 1910, and state that it is an accurate one, and one that can be conveniently carried out by the retail pharmacist. The purpose of this study was to ascertain with what ease the method could be used, and what uniformity of results could be obtained. Since they have not given all the details of manipulation, I will describe the method as I used it, my endeavor being to carry it out in all respects just as they did.

Fully grown apparently healthy cats were selected. In general these were stray cats of the city, and represented all common breeds and mixtures. They were accurately weighed, and then anæsthetized in the following manner: The animal was placed in a small box, just large enough to accommodate the body, with a small circular notch at the top of one end of a size which would just admit the neck. A cat in the box with the neck in place, the sliding lid was forced shut and held by a peg. Thus the animal was unable to withdraw its head. The anæsthetic was then given from a small copper cone carrying on a transverse screen a pad of cotton or gauze. A few drops of chloroform were placed on the cotton at the start in order to hasten this operation. As soon as the animal was unconscious this pad of cotton was replaced by another upon which only ether was dropped. The cat was then tied on an animal board (somewhat resembling the Harvard) with back down, legs outstretched, and head securely fastened in a holder. This board, supported on legs, was made so as to drain at a point near the lower (tail) end, under which a receiving vessel was placed. The animal in place, the femoral veins were dissected out and small glass cannulæ inserted. The solutions were contained in burettes, the ouabain in one and the digitalis body in the other, and were conveyed to the cannulæ by narrow catheter tubing. The injection extended, as near as could be arranged, over a period of ninety minutes.

The Ouabain Solution.

Merck's crystalline ouabain was used. The weighing was done on an accurate chemical balance, and a stock solution 1:10,000 was made in a one litre volumetric flask. For use, samples were drawn off with a pipette and diluted to the strength 1:100,000 in a narrow glass-stoppered 200 c.c. cylinder. All dilutions were made with recently prepared physiological salt solution. (0.75 per cent. NaCl.) The stock solution was kept in a cool dark cupboard, and in no case was used after two weeks old. The solution for use was made up as needed.

After running two preliminary experiments to become acquainted with the technic, a series of twenty-six experiments with ouabain was begun. The procedure and results were as follows:

The weight of the animal having been taken, the theoretical amount of solution required was calculated. Since the lethal dose

of ouabain for cats, according to Dr. Hatcher, is .0001 gramme per kilogramme of body weight, the theoretical amount of solution would be the number of cubic centimeters required, for any given animal, to supply .0001 Gm. per Kgm. And since each cubic centimeter of a 1 : 100,000 solution would contain .000.01 Gm., a 3.2 Kgm. cat, for example, would require 32 c.c. Ninety minutes being the period of injection, the proportionate part of the theoretical amount necessary to be run in each minute or two minutes, was calculated. The operator seated at the table, continued the anæsthesia by placing a small pad of gauze over the nose and supplying only sufficient ether to just keep the animal quiet. The burette having been filled and the time noted, the injection was begun, running in slowly every minute or two minutes the amount proportioned. The cat was carefully watched, particularly toward the end when the larger part of the theoretical amount had been injected. Death was usually preceded by very rapid respiration and decided convulsive movements, after which the respiration ceased to be regular and was prolonged for a few minutes only by gasps. As soon as these symptoms of approaching death appeared, the injection was stopped. If after waiting a few minutes the animal did not die, the injection was continued very slowly and with great caution. When respiration had ceased to be regular, the number of cubic centimeters of solution used and the time were noted, and before the gasping had entirely ceased the heart was exposed. In the majority of cases, rhythmic contractions of the heart had ceased. Sometimes the heart was in feeble delirium, but usually the left ventricle was still and the other chambers were feebly contracting. Out of twenty-six experiments with ouabain, sixteen with strophanthus, and twenty-seven with digitalis, only seven hearts were found beating rhythmically, and in these the contractions were very feeble. Twelve hearts showed the left ventricle in quite complete systole. It should be remembered that regular respiration had ceased from one to three minutes previous to the exposure of these hearts. In one instance under ouabain, paraldehyde was used as the anæsthetic. (1.8 c.c. per Kgm. Merck's.) Immediately upon appearance of the gasping, without opening the thorax, artificial respiration was instituted. The heart seemed to improve, and continued to beat until at the end of ten minutes one cubic centimeter more of the solution was slowly injected when it stopped. With cat No. 26 artificial respiration was supplied all through the experiment, still the animal died within the ninety

minutes, having received almost the exact theoretical amount. To accurately determine the effect of artificial respiration upon the lethal dose would of course require a large number of experiments, an interesting point, but one I have not been able to work out for lack of time and animals.

OUABAIN.

Date	Cat No.	Sex	Wt. in Kgms.	c.c. Sol.	Ouabain in Gms. per Kgm.	Time in Min.
12-16-10	1	Male	2.10	25.0	.000,119	99
12-18-10	2	Male	4.70	32.0	.000,068	70
12-21-10	3	Male	2.80	25.0	.000,089	71
12-22-10	4[1]	Male	2.00	15.0	.000,075	75
12-24-10	5	Female	1.10	11.5	.000,104	118
12-24-10	6	Male	1.80	16.8	.000,093	87
1- 4-11	7	Male	1.70	16.0	.000,094	93
1- 5-11	8	Male	2.70	16.0	.000,060	61
1-30-11	9	Female	1.19	11.2	.000,094	88
1-31-11	10	Male	2.11	22.1	.000,105	94
2- 1-11	11	Female	1.77	17.4	.000,098	95
2- 2-11	12	Female	2.33	19.6	.000,084	82
2- 2-11	13	Female	0.97	13.0	.000,134	104
2- 3-11	14	Female	2.13	27.0	.000,126	106
2- 4-11	15	Male	3.42	46.0	.000,134	106
2- 4-11	16	Female	2.43	26.5	.000,109	97
2-10-11	17	Male	2.50	23.0	.000,092	82
2-11-11	18	Male	3.27	32.7	.000,100	91
2-13-11	19	Male	2.94	25.5	.000,086	77
2-13-11	20	Male	1.81	17.5	.000,096	86
2-14-11	21	Male	2.40	20.0	.000,083	76
2-14-11	22	Female	1.87	16.0	.000,085	83
2-15-11	23	Male	2.28	22.0	.000,096	90
2-15-11	24	Female	2.25	21.0	.000,093	87
2-15-11	25	Female	1.92	13.5	.000,070	65
6-14-11	26	Female	2.38	24.0	.000,100	87

[1] Received paraldehyde instead of ether.

Two samples of strophanthus seed (Kombe) were received for testing at this time. These were reduced to No. 60 powder. Ten gram samples were placed in 150 c.c. Erlenmeyer flasks, supplied with good, tightly fitting corks, and macerated with 40 c.c. of 75 per cent. alcohol for 72 hours with occasional agitation. The content of each flask was then poured into a small narrow percolator fitted at the neck with a tight pluget of cotton. The first portion of each percolate was returned and the percolation was then allowed to pro-

ceed at the rate of 10 drops per minute. Seventy-five per cent. alcohol was added from time to time until 200 c.c. of percolate were obtained, thus finishing a 5 per cent. tincture. For injection, 1 : 6000 solutions were used. These were made in the same manner as described under ouabain. The results from eight experiments on each of these samples were as follows:

STROPHANTHUS SEED NO. B-565.

Date	Cat No.	Sex	Dilution 1:6000 Wt. in Kgms.	c.c. Sol.	1 c.c. = .000,166 gm. drug. Strophanthus in Gm.	Time
2-16-11	1	Male	2.23	16.0	.001,19	69
2-16-11	2	Male	2.65	22.0	.001,37	100
2-16-11	3	Female	2.82	26.0	.001,53	98
2-17-11	4	Male	2.29	22.9	.001,66	107
2-17-11	5	Male	2.11	24.0	.001,88	100
2-18-11	6	Male	2.98	30.0	.001,66	95
2-18-11	7	Male	3.07	31.0	.001,67	100
2-18-11	8	Female	2.04	18.0	.001,46	66

STROPHANTHUS SEED NO. B-566.

2-21-11	1	Male	2.45	26.4	.001,78	102
2-21-11	2	Male	3.17	23.0	.001,20	60
2-21-11	3	Male	1.29	11.1	.001,42	71
2-22-11	4	Male	3.00	24.0	.001,32	60
2-22-11	5	Male	3.17	25.5	.001,33	87
2-22-11	6	Female	3.14	23.5	.001,23	87
2-23-11	7	Male	3.82	29.0	.001,24	95
2-23-11	8	Male	2.93	25.0	.001,41	111

Hatcher and Brody have found after many experiments that if digitalis and the other members of the series are injected, like ouabain and strophanthus, until the animal dies, the results will usually be too high—necessitating a correction of about 20 per cent. They have therefore devised a modification of the method which gives results comparable in accuracy, they believe, to those obtained with crystalline ouabain itself. This modification is as follows:

A measured quantity of the digitalis solution (I understand about 50 per cent. of the required amount) is injected during the first period of about ten minutes. After an interval of about twenty minutes the injection is continued, substituting ouabain solution for the digitalis, until the animal dies. The difference between the

amount of ouabain actually used to complete the experiment, and the theoretical amount necessary to kill the animal in the absence of the digitalis body, represents the amount of ouabain to which the digitalis body used is equivalent. The amount of digitalis body equivalent to .0001 Gm. or one "cat unit," is then calculated.

EXAMPLE TO SHOW METHOD OF CALCULATION.

Digitalis solution = 1 : 100 — 1 c.c. = .010 Gm.
Ouabain solution = 1 : 100,000 — 1 c.c. = .000,01 Gm.

Cat weighing 3.21 Kgms. received { 30.2 c.c. digitalis sol. (.302 Gm. drug) or, .0940 Gm. drug per Kgm. body weight; 5.5 c.c. ouabain sol. (.000,055 Gm. ouabain) or, .000,017 Gm. ouabain per Kgm. of cat.

The difference between .000,017 Gm., the amount of ouabain (per Kgm.) actually used to complete the experiment, and .000,100 Gm., the theoretical amount, or one "cat unit," which would have been required in the absence of the digitalis body, is .000,083 Gm.

.094 Gm. of the digitalis is therefore equivalent to .000,083 Gm. ouabain, or .094 Gm. of the digitalis = 83 per cent. of one "cat unit."

.113 Gm. of the digitalis would then be equivalent to one "cat unit."

F. E. DIGITALIS.

No. 405467.

Digitalis dilution 1:100
Ouabain dilution 1:100,000

Date	Cat No.	Sex	Wt. in Kgms.	c.c. Dig. Sol.	c.c. Ouabain Sol.	Equiv. in Gm. of 1 Cat Unit	Time in Min.
2-27-11	1	Female	3.21	30.2	5.5	.113,5	95
2-27-11	2	Male	2.88	25.0	3.0	.096,8	61
2-27-11	3	Male	2.87	25.0	7.0	.115,2	100

F. E. DIGITALIS.

No. 416233.

5- 8-11	1	Male	2.33	14.0	5.2	.077,3	66
5- 8-11	2	Female	2.18	12.0	3.6	.065,8	65
5- 9-11	3	Male	2.07	11.0	4.6	.068,2	80
5- 9-11	4	Female	1.83	10.0	6.7	.086,1	73
5-10-11	5	Male	2.21	11.1	6.0	.068,8	97
5-10-11	6	Male	2.40	14.0	8.0	.087,4	82

F. E. DIGITALIS.

No. 335929.

5-11-11	1	Female	1.72	10.0	3.5	.072,8	79
5-11-11	2	Male	3.18	15.0	21.0	.138,7	114
5-11-11	3	Female	1.75	11.7	9.0	.137,5	100
5-12-11	4	Female	1.89	10.0	10.0	.112,3	90
5-13-11	5	Female [1]	2.15	10.0	15.0	.153,4	155
5-15-11	6	Female [1]	2.55	12.0	25.5	.522,7	114
5-15-11	7	Female [1]	1.82	12.0	12.0	.193,5	80
5-16-11	8	Male	3.00	16.0	17.5	.127,9	115
5-17-11	9	Female [1]	2.90	17.5	9.7	.090,6	75
5-18-11	10	Male	2.46	16.0	7.0	.090,8	75
5-18-11	11	Female	1.98	11.0	8.0	.093,2	85

[1] In varying stages of lactation.

TR. DIGITALIS NO. 2-B.

5-22-11	1	Female	2.11	13.0	3.5	.073,2	61
5-23-11	2	Male	2.89	14.0	16.5	.112,6	95
5-23-11	3	Female [1]	2.35	13.0	15.0	.154,2	85
5-24-11	4	Male	2.83	17.0	3.0	.067,1	111
5-24-11	5	Female [2]	2.46	15.0	14.0	.141,4	106
5-24-11	6	Male	2.30	16.4	8.0	.109,3	81
5-25-11	7	Female	3.00	16.0	7.5	.071,1	73

[1] Lactating.
[2] Apparently in period immediately following lactation. Glands were still enlarged, but not functuating.

ASSAYS ON FOREGOING PREPARATIONS BY OTHER METHODS.

ONE-HOUR FROG HEART METHOD. VARIETY RANA PIPIENS. TEMPERATURE 20° C.

STROPHANTHUS SEED B-565.

Weight of frog in Grammes	Dose per Gramme	Result
36.5	.000,006,0	Stopped
40.8	.000,005,0	"
15.1	.000,005,0	"
28.1	.000,004,0	"
39.6	.000,004,0	"
23.0	.000,004,0	"
43.8	.000,003,5	"
36.4	.000,003,5	"
48.7	.000,003,5	Beating
35.2	.000,003,0	"
19.4	.000,003,0	"

STROPHANTHUS SEED B-566.

18.2	.000,006,0	Stopped
20.6	.000,005,0	"
23.6	.000,005,0	"
15.4	.000,005,0	"
43.7	.000,005,0	"
18.1	.000,004,0	"
18.5	.000,004,0	"
25.8	.000,004,0	"
28.0	.000,004,0	Beating
28.8	.000,004,0	Stopped
34.4	.000,004,0	"
37.2	.000,003,5	"
45.3	.000,003,5	Beating
49.0	.000,003,5	"
37.6	.000,003,0	"

GUINEA PIG METHOD.

F. E. DIGITALIS No. 416233.

Weight of pig in Grammes	Dose per Gramme	Result
709	.000,5	Recovered
786	.000,5	"
825	.000,5	"
467	.000,5	Died
524	.000,5	"
694	.000,6	Recovered
701	.000,6	"
814	.000,6	Died
835	.000,6	"
744	.000,7	"
517	.000,7	"
481	.000,8	"

F. E. DIGITALIS No. 335929.

750	.000,4	Recovered
340	.000,4	"
736	.000,4	"
680	.000,4	"
815	.000,5	"
630	.000,5	"
737	.000,6	"
772	.000,6	"
737	.000,7	Died
725	.000,7	"
531	.000,7	"
552	.000,7	Recovered
731	.000,8	"
538	.000,8	Died
375	.000,8	"

ONE-HOUR FROG HEART METHOD. VARIETY RANA PIPIENS. TEMP. 20° C.

F. E. DIGITALIS.

No. 416233.

Weight of frog in Grammes	Dose per Gramme	Result
40.9	.000,50	Beating
42.9	.000,60	"
39.1	.000,60	"
34.0	.000,70	"
46.5	.000,70	"
42.2	.000,75	"
50.8	.000,80	"
38.8	.000,80	"
31.2	.000,90	"
38.2	.000,90	Stopped
31.4	.001,00	"
35.5	.001,00	"

F. E. DIGITALIS.

No. 335929.

28.9	.000,90	Stopped
22.0	.000,80	"
21.0	.000,70	"
27.6	.000,70	"
23.0	.000,70	"
30.5	.000,70	"
42.9	.000,70	"
19.3	.000,65	Beating
20.2	.000,60	Stopped
23.5	.000,60	"
36.5	.000,60	"
37.4	.000,60	Beating
36.5	.000,50	"

The assays of these preparations by other methods have been inserted here, with the belief that they will be of some interest to the reader if closely analyzed, although no decided conclusions can be drawn from so small a number. Considering F. E. Digitalis No. 416233 and No. 335929 by the guinea pig and frog heart methods, it will be seen that while they show almost the same result on the guinea pig, there is a decided difference on the frog's heart. A lack of relationship in the results obtained by these two methods has been observed by others. Remembering that these fluids test the same on the guinea pig, consider the assays by the

cat method where No. 416233 is decidedly more active than No. 335929, the reverse of what was found by the frog heart method.

Attention should be called to the lot of animals used for No. 335929, which was perhaps the least suitable of any. It may be noticed that the greater number were females, varying considerably in size, some being in different stages of lactation. (No. 6 was in the early stage and had exceptionally large glands.) The males were all large and the results, perhaps a coincidence, varied somewhat in relation to the weight:

	Weight	Result
No. 2	3.18 Kgms.	.140,3
No. 8	3.00 Kgms.	.127,8
No. 10	2.46 Kgms.	.090,8

The assays on the two samples of strophanthus seed are almost identical by the frog heart method, and show but a small difference by the cat method.

Discussion.

Animals.—Hatcher and Brody selected cats in preference to dogs, and I believe rabbits, for several reasons, namely: "Accuracy afforded, facility with which they may be obtained, ease with which they may be handled, cheapness, and the fact that their use does not affect the sensibilities of the sentimental portion of the community to the same extent that the employment of the dog does." Having used no other animals for this particular method, I cannot remark on the point of accuracy. My experience has been that there is little in their favor regarding cost, all things considered. Cats are easily handled, though to my mind are no more so than dogs, or rabbits, except that in the case of the latter greater care is necessary in regard to any dissection or the giving of anæsthetics. I have found them far more difficult to obtain than rabbits and hardly less so than dogs. Whether their use affects the sensibilities of the sentimental portion of the community less than that of the dog seems questionable. At any rate, the use of cats certainly does affect the sensibilities of many people, and the procuring of a sufficient number of animals for this piece of work has been the source of considerable trouble. And for a manufacturing plant of this size, to secure enough cats to carry out the routine assays on the several members of the digitalis series, would be a practical impossibility. If some easily procurable animal such as the rabbit could be used for

this work, then one great difficulty would be removed. This point is of immense importance to the manufacturer by whom nearly all of the practical physiological assaying will always be done.

Having experienced difficulty in buying cats, an attempt was made at this laboratory to raise them, but this met with poor success. It has seemed that only under the very best conditions can cats be kept well for any considerable length of time. It has been our not infrequent experience that cats will refuse sweet milk and raw beef for some time after having been received, and while an abundance of food has been supplied, our cats have usually lost in weight.

When cats are needed for this work they should be made to fast for at least twenty-four hours, as otherwise vomiting will frequently occur, particularly under digitalis. Greater accuracy can also be obtained in regard to the weight.

Lactating animals cannot be depended upon as they seem to possess a greater tolerance for the drug, the degree depending on the stage of lactation.

The Period and Rate of Injection. The lethal dose of any of the digitalis bodies cannot, of course, be told at the outset. This is indeed the figure sought. Therefore, " 50 per cent. of the lethal dose " is a quantity which can only be widely approximated by one's experience with the given preparation. Whether this point in itself is a matter of great importance, within certain wide limits, I am unable to say. It would seem to be of importance, however, that the injection of all of these drugs be proportioned as evenly as possible over the ninety minutes. After one has injected an amount of digitalis, for example, and has waited the twenty minutes, he is ready to proceed with the ouabain solution. Since he does not know the value of the digitalis, he does not know, consequently, how much ouabain solution it will be necessary to inject during the following period of one hour. And not knowing this point, he is unable to judge how rapidly to inject. If he calculates on 5 c.c. when 10 c.c. would actually be required, then he will come to the end of the ninety-minute period with the animal still alive, and he must cautiously proceed with the probable result that one hundred and five minutes or so will be covered in completing the experiment. And having injected at a slower rate possibly a larger amount of ouabain may have been required. On the other hand, if he calculates on 10 c.c. when only 5 c.c. are necessary, he may kill the animal before the end of the period—perhaps in seventy-five minutes. And having

injected at a more rapid rate possibly less ouabain may have been used than would have been under normal conditions.

It might be remarked that the first experiment would furnish these points. This might be true, still, it might happen that the results from number one would be exceptional. Then the operator would be thrown off on number two, and when he found the results from number two quite different, number three would be necessary in order to tell which was more nearly correct.

If these points are of no importance then it would seem that the time limit of ninety minutes would be of no importance.

Number of Animals and Time.—In general it would seem that at least three experiments would be necessary in order to determine with confidence the strength of a preparation. If two out of three results checked quite closely, as under F. E. Digitalis No. 405467 (.113,5, .115,2), that number might be sufficient. Under strophanthus seed No. B-565, however, the results show a gradual increase up to the sixth experiment (.001,19, .001,37, .001,53, .001,66, .001,88), and under F. E. Digitalis No. 416233, results Nos. 1, 4, and 6 check each other rather closely (.077,3, .086,1, .087,4), and Nos. 2, 3, and 5 at a different figure check each other even more closely (.065,8, .068,2, .068,8).

If three or four experiments were sufficient, then an assay could be made in one day, a point in favor of the method. This would require one person's entire time and attention for the four and a half or six hours, besides part of the time of an assistant. At that, more actual time would be required than for any of the other methods.

Ease of Manipulation and Accuracy.—The method seems simple, and still, all points considered, it is the most difficult of all with which I am acquainted.

My results have been quite disappointing. They show variations for the different preparations, as follows:

Ouabain	123.3 per cent.
Excluding results Nos. 2, 4, 8, and 25	61.4 per cent.
Strophanthus Seed No. B-565	57.9 per cent.
Strophanthus Seed No. B-566	48.3 per cent.
F. E. Digitalis No. 405467	19.0 per cent.
F. E. Digitalis No. 416233	32.8 per cent.
F. E. Digitalis No. 335929 (excluding lactating animals)	90.5 per cent.
Excluding lactating animals and No. 1	53.0 per cent.
Tr. Digitalis No. 2-B (excluding Nos. 3 and 5)	67.8 per cent.

My results with crystalline ouabain would indicate that the lethal dose of this substance varies considerably with different animals. It seems, then, irrational to estimate the value of a preparation of digitalis, from its supposed equivalent of a body which is in itself, for any given animals, an unknown quantity. The authors of this method claim that crystalline ouabain will exactly replace digitalis in regard to its toxicity on the cat. It seems to me, however, that there might be some variance in its power to exactly replace different samples of digitalis depending on the proportion of active principles present and the conditions of these principles, whether or not decomposed. Since the amount of digitalis to be injected which will represent 50–75 per cent. of the required amount is an unknown quantity, it necessarily follows that the amount of ouabain required to complete the experiment, even if its toxicity could be exactly known, is an unknown quantity. Therefore, not knowing the amount of ouabain required, the rate of injection, which probably plays an important part, cannot be known. Lastly, the time required to kill, being dependent on the rate of injection, constitutes another unknown factor. So, when testing a sample of digitalis, one has to deal with six or more unknown factors. This requires an operator of considerable experience and skill.

Summary.

Considering the results of this work, together with my experience with the other methods, I am led to make the following statements in conclusion:

The cat method of Hatcher and Brody is unquestionably the most complicated and difficult of all the American methods, requiring an operator of considerable experience in animal experimentation.

It is *not* a method that will be found convenient and generally serviceable by the retail pharmacist.

It is more time-consuming than the other methods, requiring constant attention when started.

The item of expense, like that of the guinea-pig method, is decidedly in its disfavor.

The procuring of a sufficient number of suitable animals is a practical impossibility for the manufacturing pharmacist having a large number of preparations to test. This may also be the source of much unpleasantness and trouble.

Lactating animals cannot be depended upon as they seem to possess a greater tolerance for the drug, the degree depending on the stage of lactation.

While individual results will not infrequently check each other very closely, considering the results of an entire assay, great variations will often be observed, amounting in some cases to more than 100 per cent.

When testing a preparation one has to consider six or more unknown factors, namely:

1. Toxicity of ouabain.
2. Power of ouabain to exactly replace the digitalis bodies.
3. Amount of digitalis to be injected.
4. Amount of ouabain to be injected.
5. Rate of injection.
6. Time.

This method has perhaps one point of superiority over all others in that the matter of absorption is entirely eliminated.

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ABSTRACTS OF PAPERS READ AT THE BRITISH PHARMACEUTICAL CONFERENCE

BY JOHN K. THUM, PH.G. Pharmacist at German Hospital, Philadelphia.

Portsmouth, the great naval port of the United Kingdom, was the scene of the forty-eighth anniversary of the foundation of the British Pharmaceutical Conference.

The sessions opened on Tuesday morning, July 25, 1911. Mr. William Frederick Wells, the President of the Conference, who is one of the best known pharmaceutical chemists of Ireland, and whose knowledge of the laws pertaining to pharmacy in the Emerald Isle is most comprehensive, devoted a considerable portion of his his presidential address to a discussion of the laws appertaining to pharmacy in the United Kingdom.

He commenced his address by speaking feelingly of the irreparable loss which British pharmacy sustained through the death of

John Attfield. Professor Attfield was President of the Conference for two years, in 1882 and 1883. He was one of the best minds in the scientific circles of pharmacy, a leader, with great ability, and untiring energy in the cause of pharmacy. "As a teacher he had great opportunities of bringing the best out of his pupils."

Mr. Wells then went on to speak of the craze for cheapness in the purchase of medicines by the public; medical records, he states, show that many valuable lives are sacrificed by this craze for low prices and the use of worthless drugs.

Specialization is the tendency of modern times, and he argues that if pharmacists want success in their calling they must specialize. The confidence of the public is only obtained by those who are best fitted to serve it efficiently. "The moment pharmacy is lowered to the level of a general business, as is being done so largely in our day by department stores and by limited companies of persons without any knowledge of pharmacy, whose sole object is to 'make money—honestly, if ye can, but make money'—then the fine art of professional dispensing is lost, and in many cases the public health suffers."

He then proceeded to deal with his chief theme, namely, the pharmacy laws of the United Kingdom. The Pharmacy and Poison laws, he states, were passed solely for the protection of the King's subjects and not for the benefit of the dispensing chemist. He then contrasts the laws with those of French and German Pharmacy. The essential difference in principle between their own pharmacy laws and those of France is that the French laws give the pharmacist a definite place in the community, certain services to perform for the community, and ensure that none shall poach upon the preserves fenced by these laws. No one may commence the study of pharmacy in France until satisfactory proof is given that the applicant's preliminary training is adequate. The requirement being a degree in Arts, Mr. Wells calls attention to the fact that the French law confers on pharmacists the sole right to dispense medical prescriptions, the only exceptions being in remote villages, where no pharmacists are in business, and only then are doctors allowed to dispense medicines. In discussing the German pharmacy laws the interesting fact was brought out that a custom exists there which is unknown in Great Britain, France or our own country, of strictly limiting the number of pharmacies, each pharmacy throughout the empire being licensed by the State. The result is that an apotheker cannot start business until a vacancy for a pharmacy occurs and he obtains

or purchases the concession to carry on the business of an old-established pharmacy or to open a new one where the growth of the population warrants, the State granting a new concession.

Mr. Wells also discussed several other acts or laws of Great Britain which are closely connected with pharmacy, the most important the Sale of Food and Drugs Act. He states that there is room for improvement in this act. It should be amended so as to make conviction certain when fraud is clear; too many technicalities are available under which offenders escape punishment.

Among the interesting communications brought to the attention of the Conference were the following papers:

Further Note on Podophyllum Emodi.

By John C. Unmey.

The writer mentions the difference of opinion regarding the therapeutic value of the resins of the two species of podophyllum—the American, *Podophyllum peltatum,* and the Indian, *Podophyllum Emodi.* He thinks this matter should be settled before the next British Pharmacopœia is issued.

The result of chemical and physiological tests brings him to the conclusion that a reasonable method of judging the resin is by means of podophyllotoxin assay. He gives such a method.

The Supposed Loss of Morphine in the Preparation of Tincture of Opium.

By E. H. Farr and R. Wright.

The authors state that from time to time statements have been made to the effect that in the conversion of opium into extract or tincture a loss of alkaloid results, or, rather, that the quantity of morphine shown by the official assay of a sample of opium is always greater than the amount found in the finished product, even when the utmost care has been taken to secure perfect exhaustion of the drug. The authors carried out some experiments with the view of testing the accuracy of these statements. They also give their method. They find that when official methods are followed throughout there is always a loss of morphine. They think that the loss is probably due to occlusion of the alkaloid, making its complete extraction by water or alcohol a matter of much difficulty.

Extract of Indian Hemp.

By Harold Deane.

The author says that as it is generally admitted that the resinous portion of the extract contains the active principle, and therefore extracts which are practically pure resin may be expected to be therapeutically more active. The author gives a simple and economical method for obtaining such an extract, which consists in washing away the brown extractive with warm water, after the alcohol has been distilled off.

Note on Spirit of Sal Volatile.

By E. W. Pollard.

For the preparation of sal volatile the writer recommends the following:

Oil of nutmeg	4½ drachms
Oil of lemon	6½ drachms
Water	2 pints

Distil one pint, mix with six pints of alcohol.

Dissolve ammonium carbonate 4 oz., in strong solution of ammonia 8 oz., water 9 oz., by the aid of gentle heat. Add this solution to the alcoholic solution of oils. In our opinion there is no necessity for even "gentle heat."

A Suggested Standard for Thyroideum Siccum.

By Reginald R. Bennett.

As it is agreed among most pharmacists that the activity of thyroid is dependent upon the combined iodine present the author of this paper thinks that an iodine standard should be made official. He gives a method for determining the iodine which is practically the same as Baumann. He also states that an iodine standard of 0.15 per cent. could be adopted for thyroideum siccum without in any way unduly harassing the manufacturer.

Linimentum Ammoniæ.

By F. H. Alcock.

The author briefly mentioned the various devices used to prevent solidification caking, and partial separation, of linimentum ammoniæ. As a result of experiments made by him he advises the following

method, which consists in reducing the amount of water in the preparation to a minimum, as giving effectual results:

Almond oil	3 ozs.
Olive oil	8 ozs.
Strong solution of ammonia (0.880 of commerce)	1 oz.

Note on Spirit of Nitrous Ether.

By D. B. Dott.

The author makes the proposition that no spirit of nitrous ether should be kept in stock at all because of liability to deterioration. As is well known this loss is occasioned by the volatilization of ethyl nitrite. He advises the use of two solutions, like Fehling No. 1 and No. 2 for the extemporaneous preparation of this spirit; the procedure being to mix a ½ dram of solution of sodium nitrite with 7½ drams of acidified alcohol to make 1 oz. of spirit of nitrous ether. He also suggests the use of lactic acid for acidifying the alcohol.

Note on Bartsia Odontites.

By H. Finnemore and G. E. Town.

Bartsia Odontites is a very common wayside plant of the natural order of *Scrophulariaceæ,* and although no toxicity has been ascribed to it, it is well known to be avoided by cattle. The authors bearing in mind the fact that plants botanically related often contain similar chemical constituents, it occurred to them that this relative of digitalis might possibly be worthy of pharmacological as well as chemical investigation.

Fourteen pounds of the whole plant were collected when in flower, dried in the sun, and completely extracted with hot alcohol in a continuous extraction apparatus. The resulting solution was concentrated and a sample tested on frogs. It was shown that it had no poisonous or digitalis-like effect. On allowing the alcohol solution to stand twenty-four hours a fairly large amount of crystalline matter separated in a nearly pure condition. The crystals proved to be mannitol. Identification was obtained by their composition, melting-point, and by their acetyl derivative.

Other papers read at Conference were: "The Moisture and Ash-content of Medicinal Extracts," by K. C. Allen and Theo. Brewis; "Note on Arsenates of Strychnine," by D. B. Dott; "Note on Strychnine Hypophosphite," by D. B. Dott; "Note on Solution of

Sodium Ethylate," by H. Finnemore; "An Experiment in Peppermint Culture," by H. John Henderson; "The Composition of Diabetic Foods," by F. W. F. Arnaud; "Note on the Constitution of Commercial Bismuth Subchloride," by J. Bristowe P. Harrison; "White Precipitate and the Analysis of White Precipitate Ointment," by G. D. Elsdon.

PRESIDENT TAFT'S ACTION UPON THE RECOMMENDATIONS OF THE COMMITTEE ON PERSONNEL OF THE U. S. DEPARTMENT OF AGRICULTURE.

President Taft's opinion of Doctor Harvey W. Wiley and his conduct of the Bureau of Chemistry (see this JOURNAL, pp. 381 and 388) has been in the hands of the public since September 16, 1911. The President's opinion, as embodied in his letter to the Secretary of the U. S. Department of Agriculture, carries no word of criticism, but many a word of praise.

Speaking of the Congressional investigation into the Department of Agriculture, Mr. Taft says:

"The broader issues raised by the investigation which have a much weightier relation than this one to the general efficiency of the department may require much more radical action than the question I have considered and decided.

"The nub of the charge by the personnel board was that Doctor Wiley, Doctor Kebler, Doctor Bigelow and Doctor Rusby in effect conspired to put on the record a contract for a general employment of Doctor Rusby's services for $1,600 a year, but actually and secretly made a contract with him by which he was only to do enough work during the year for the $1600 to secure him a compensation of $20 a day and that this was done in deliberate and defiant violation of the law was interpreted by the Attorney-General in the opinion already referred to, in which he held that Congress had limited the compensation of experts to $9 a day.

"After you submitted to me the report of the personnel board I asked the Attorney General to examine it and give me his opinion in respect to the matter. He did so and advised me that the recommendations of the personnel board ought to be carried out. In connection with his recommendations, he invited attention to a clause in the appropriation bill of March, 1907, still in force, that enjoins upon the head of each department the duty of exacting from the

employes in that department who are under an annual salary labor amounting to seven hours a day.

"An examination of the records satisfied me that the questions had not been presented to the persons involved in such a way as to enable them to make full defense. They had only been called as witnesses, and cross-examined without a full understanding that they were under trial which might involve their dismissal. Accordingly I directed you to submit the whole record to each one of the persons charged and invite from him an answer.

"The answer of Doctor Wiley specifically denies that he evet saw the correspondence between Doctor Kebler and Doctor Rusby or that he ever consciously entered into an agreement by which Doctor Rusby was in effect to receive compensation at a rate in excess of that prescribed by the statute as interpreted by the Attorney-General.

"The truth is, it appears from the answers of Doctor Wiley, Doctor Kebler and Doctor Bigelow that there had been a good many precedents in the department which seemed to justify the employment of Doctor Rusby at an annual salary when it was not expected that his entire time would be taken up. This was the case with respect to the employment of what was known as the Remsen Board.

"Solicitor McCabe, to whom I referred the question of precedents made in the case, replied that in the practice of the department the clause in the appropriation act of March 5, 1898, had been held to have no application to the employment of experts outside of Washington.

"It is necessary fully to understand this difference between the attitude of the department toward an employment at an annual salary of this kind, and the opinion of the Attorney-General in this matter, because if Doctor Wiley and his associates had understood that the $1600 annual salary required them to exact from Doctor Rusby seven hours a day for all the work days of the year, then, of course, his employment must have been known by them to be illegal and under the circumstances, to be only a cover for a different contract of employment; but if they understood, as seems to have been the case generally in the department, that such an employment at an annual salary might be entered into with experts of this kind, and only subject the experts to an obligation to work for the department whenever called upon, with the understanding that they had

some other vocation to which their chief attention was given, it clearly reconciled the action of Doctor Wiley with a desire to comply with the law.

"The recommendation of the Attorney-General given to me was upon only part of the evidence, and hence his judgment was different, doubtless, from what it would have been if he had had the whole record before him, as I have now.

"It seems fairly clear that Doctor Wiley, after an examination of the records, concluded that the employment of Doctor Rusby at $9 a day for laboratory work and $50 a day for court work would amount to $1600 a year if the department called on him whenever they needed him, and that it was this arrangement to which you consented. In Doctor Kebler's anxiety to induce Doctor Rusby to accept the new terms of employment he certainly betrayed a willingness to construe the contract of employment of Doctor Rusby at $1600 a year in one way to reconcile it with the law and in another way to satisfy Doctor Rusby in his wish to secure $20 a day, and I think he ought to be reprimanded for his disingenuous conduct in writing such letters as he did. He said that he did not intend to violate the statute as interpreted by the Attorney-General, and, indeed, that he did not know exactly what the ruling was; but whether he did or not, the language of his letters does not have a commendable tone and suggests a willingness to resort to evasion that calls for official reproof.

"Here is the pure food act which is of the highest importance to enforce, and in respect to which the interests opposed to its enforcement are likely to have all the money at their command needed to secure the most effective expert evidence. The Government ought not to be at a disadvantage in this regard and one cannot withhold one's sympathy with an earnest effort by Doctor Wiley to pay proper compensation and secure expert assistance in the enforcement of so important a statute, certainly in the beginning when the questions arising under it are of capital importance to the public.

"If this were a knowing, wilful, deliberate effort to evade the statute as construed by the Attorney-General, accompanied by a scheme to conceal the evasion and violation, I should think the punishment recommended by the personnel board and concurred in by the Attorney-General was none too great; but an examination of the whole case satisfies me that a different construction ought to

be put upon what was done; that the evidence does not show that Doctor Wiley was a party to the correspondence or the letters upon which the chief charge is sounded, and that his action in the matter was only in accord with previous precedents in the department which justified him in doing what he did.

"With respect to the other persons charged, I find an over zeal in Doctor Kebler and Doctor Bigelow, which prompted a disingenuous method of squaring Doctor Rusby's desire for what he thought was adequate compensation with the contract which you and Doctor Wiley were willing to make with him and that for this Doctor Kebler and Doctor Bigelow should be reprimanded by you. So far as Doctor Rusby is concerned with respect to this particular contract I do not find him at fault. For purposes of punishment or dismissal, I cannot charge him with knowledge of the legal difficulties involved in his employment. I examined the record in this case a number of weeks ago and I reached the conclusion which I have stated here, but meantime, a committee of the House of Representatives deemed it proper to institute an investigation into the Department of Agriculture, and especially into the Bureau of Chemistry and its relation to the department generally.

"It seemed to me, under these conditions that perhaps it was wiser for me to delay until the investigation was completed and the report of the committee made. The committee has not made a report, although I believe the evidence has been substantially closed and will not do so until the next session of Congress.

"Further consideration satisfies me that there are much broader questions involved in the investigation and the evidence there brought out than in the present charge, which is narrow and definite and can now be properly disposed of. The broader issues raised by the investigation which have a much weightier relation than this one to the general efficiency of the department may require much more radical action than the question I have here considered and decided.

"There is another charge against Doctor Rusby for securing the appointment, on the common laborers' rolls, of a physician and expert whom he could use to do his work at a small stipend, when he himself was called away in other employment. I regret to say that the arrangement which Doctor Rusby thus made is not especially creditable to him and shakes in some degree one's confidence in his avowed wish to make personal pecuniary sacrifice in the public inter-

est for the enforcement of the pure food law. But Doctor Rusby's position as an expert of high standing is such that I do not think that any more than this expression of opinion should be imposed as penalty. My information is that the Government needs his services, that he has already rendered valuable aid and that the error referred to committed by him should not call for any further action or remark.

"You will communicate the result to the personnel board, and also to the persons charged. Sincerely yours,

"WILLIAM H. TAFT."

THE NEW ADMISSIONS AND DELETIONS TO THE U. S. PHARMACOPŒIA IX.

At the Boston meeting of the American Pharmaceutical Association, Prof. Joseph P. Remington, Chairman of the Revision Committee of the U. S. Pharmacopœia, submitted the names of the articles proposed for admission and deletion to the 9th revision of the U. S. Pharmacopœia. As most of the substances are retained, the names of only those articles which are "dropped" from the Pharmacopœia and those have been proposed for admission are printed at this time.

LIST OF ARTICLES DROPPED FROM THE PHARMACOPŒIA.

Acetum Opii
Acidum Camphoricum
Acidum Sulphurosum
Alumini Sulphas
Argenti Nitras Mitigatus
Bismuthi Citras
Bismuthi et Ammonii Citras
Calamus
Cassia Fistula
Cataplasma Kaolini
Ceratum Camphoræ
Ceratum Plumbi Subacetatis
Cerii Oxalas
Chimaphila
Chirata
Cinnaldehydum
Colchici Cormus
Collodium Stypticum
Confectio Sennæ
Conium
Cusso
Cypripedium
Emplastrum Hydrargyri
Emplastrum Opii
Emplastrum Saponis
Emulsum Chloroformi
Emulsum Olei Morrhuæ cuf Hypophosphitibus
Extractum Colchici Cormi
Extractum Digitalis
Extractum Hæmatoxyli
Extractum Krameriæ
Extractum Leptandræ
Extractum Malti
Extractum Scopolæ
Extractum Sumbul

Ferri Citras
Ferri et Ammonii Sulphas
Ferri et Ammonii Tartras
Ferri et Potassii Tartras
Ferri et Strychninæ Citras
Ferri Hydroxidum
Ferri Hypophosphis
Ficus
Fluidextractum Calami
Fluidextractum Calumbæ
Fluidextractum Chimaphilæ
Fluidextractum Chiratæ
Fluidextractum Conii
Fluidextractum Cubebæ
Fluidextractum Cypripedii
Fluidextractum Digitalis
Fluidextractum Euonymi
Fluidextractum Eupatorii
Fluidextractum Geranii
Fluidextractum Lappæ
Fluidextractum Leptandræ
Fluidextractum Lupulini
Fluidextractum Matico
Fluidextractum Mezerei
Fluidextractum Pareiræ
Fluidextractum Phytolaccæ
Fluidextractum Quassiæ
Fluidextractum Quercus
Fluidextractum Quillajæ
Fluidextractum Rosæ
Fluidextractum Rubi
Fluidextractum Sabinæ
Fluidextractum Sanguinariæ
Fluidextractum Scopolæ
Fluidextractum Scutellaria
Fluidextractum Stillingiæ
Fluidextractum Stramonii
Fluidextractum Veratri
Geranium
Glyceritum Ferri, Quininæ et Strychninæ Phosphatum
Hamamelidis Cortex
Hedeoma
Hyoscyaminæ Sulphas
Infusum Pruni Virginianæ
Iodolum
Lappa
Lithii Benzoas
Lithii Salicylas
Mangani Sulphas
Mastiche
Matico
Mistura Ferri Composita
Mistura Rhei et Sodæ
Mucilago Ulmi
Naphthalenum
Oleatum Quininæ
Oleoresina Lupulini
Oleum Adipis
Oleum Aethereum
Oleum Chenopodii
Oleum Copaibæ
Oleum Erigonerontis
Oleum Sabinæ
Pilulæ Aloes et Mastiches
Pilulæ Aloes et Myrrhæ
Pilulæ Laxativæ Compositæ
Pilulæ Opii
Pilulæ Podophylli, Belladonnæ et Capsici
Prunum
Plumbi Iodidum
Plumbi Nitras
Potassii Sulphas
Prunum
Pulvis Morphinæ Compositus
Quercus
Quillaja
Rubus
Sabina
Santonica
Scammonium
Scoparius
Scutellaria
Sodii Bisulphis
Sodii Nitras
Sodii Pyrophosphas
Spiritus Aetheris Compositus
Sulphuris Iodidum
Syrupus Ferri, Quininæ et Strychninæ Phosphatum
Syrupus Hypophospitum Compositus
Syrupus Krameriæ
Syrupus Rubi
Tamarindus
Tinctura Aloes et Myrrhæ

Tinctura Cardamomi
Tinctura Gallæ
Tinctura Ipecacuanhæ et Opii
Tincturæ Herbarum Recentium
Trochisci Gambir
Trochisci Glycyrrhizæ et Opii
Trochisci Krameriæ
Trochisci Santonini
Unguentum Gallæ
Unguentum Hydrargyri Oxidi Rubri
Unguentum Potassii Iodidi
Unguentum Veratrinæ
Unguentum Zinci Stearatis
Viburnum Opulus
Vinum Album
Vinum Cocæ
Vinum Colchici Seminis
Vinum Ergotæ
Vinum Ferri
Vinum Ferri Amarum
Vinum Ipecacuanhæ
Vinum Opii
Vinum Rubrum
Zea
Zinci Bromidum
Zinci Iodidum

NEW ARTICLES PROPOSED FOR ADMISSION TO THE U. S. PHARMACOPŒIA IX.

Ammonium Bifluoride
Antitetanic Serum
Apiol
Aspidospermine
Bismuth Beta-Naphthol
Buchu (Long)
Caffeine Sodio-Benzoate
Calcium Chloride (Hydrated Crystals)
Calcium Glycerophosphate
Calcium Lactate
Carbonic Acid (Compressed)
Condurango
Creosote Carbonate
Crocus
Diacetyl-Morphine
Diacetyl-Morphine Hydrochloride
Diastase
Emplastrum Cantharidis
Erythrol Tetranitrate
Fluorescein
Hydrastine Hydrochloride
Mercury Salicylate
Milk of Magnesia
Milk of Bismuth
Oxygen (Compressed)
Picric Acid
Phenolphthalein
Pine Needle Oil
Potassa Sulphurata
Quinine and Urea Hydrochloride
Saccharin Sodium Salt
Sodium Cacodylate
Sodium Glycerophosphate
Sodium Perborate
Solution of Hydrogen Dioxide (30 per cent.)
Theobromine Sodio-Salicylate
Trioxymethylene.
Uranium Nitrate
Vaccine Virus

There are thirty-eight articles still under consideration for admission.